# "Phytochemical and Pharmacological Evaluation of Seeds of *Artocarpus hirsutus* in the management of metabolic syndrome."

**Submitted By**

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# CERTIFICATE

Certified that this Thesis titled **"Phytochemical and Pharmacological Evaluation of Seeds of *Artocarpus hirsutus* in the management of metabolic syndrome"**.is the bonafide work of **SUMA V K**, who carried out the research under my supervision. Certified further that to the best of my knowledge the work reported herein does not form part of any other thesis or dissertation on the basis if which a degree or award was conferred on an earlier occasion on this or any other scholar.

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## DECLARATION

This is to certify that the synopsis of the Thesis entitled **"Phytochemical and Pharmacological Evaluation of Seeds of *Artocarpus hirsutus* in the management of metabolic syndrome"** is a bonafide research work done by **SUMA.V.K** (Reg no: 8815001), a part time research scholar, in the Department of medicine , during the years October 2014 to December 2019.

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## INTRODUCTION

World Health Organization (WHO) defines traditional medicine as:"Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness."[1]

The plants may be regarded as a biosynthetic laboratory not only for the chemical compounds like carbohydrates, proteins and lipids that are consumed as food by humans, but also for a large number of other multiple compounds like glycosides, alkaloids, volatile oils, tannins, etc. that exerts different physiological effects on human body. Those compounds that are responsible for therapeutic effects are usually the secondary metabolites, mentioned above. Systemic studies of crude drugs are embraced through the consideration of both primary and secondary metabolites derived from plant as a result of plant metabolism.[2]

Since the beginning of civilization, the medicinal plants have been used by humans for their therapeutic values. Nature is alwaysa source of medicinal agents for human beings and animals. An impressive number of modern drugs have been isolated from plant sources. Numerous isolations are based on the uses of therapeutic agents utilized in traditional medicine. Consumption of medicines derived from plants is wide spread and increase significantly in both traditional and modern methods of medicine. According to World Health Organization more than 80% of population in developing countries depends primarily on plant based medicines for their basic healthcare needs. [3]

The genus *Artocarpus* (Moraceae) comprises about 50 species of evergreen and deciduous trees. Economically, the genus is of appreciable importance as a source of edible fruit, yield fairly good timber and is widely used in folk medicines. Ethno-pharmacological uses of *Artocarpus* speciesinclude treatment against inflammation,

malarial fever, diarrhoea, and diabetes and tapeworm infection. *Artocarpus* species are rich in phenolic compounds including flavonoids, stilbenoids, arylbenzofurons and jacalin, a lectin. The extracts and metabolites of *Artocarpus* particularly those from leaves, bark, stem and fruit possess several useful bio-active compounds. In recent times additional data are available on exploitation of these compounds in the various biological activities including antibacterial, anti-tubercular, anti-viral, anti-fungal, anti-platelet, anti-arthritic, tyrosinase inhibition and cyto-toxic properties. Several pharmacological studies of the natural products from *Artocarpus* have conclusively established their mode of action in treatment of various diseases and other health benefits.

Metabolic syndrome is a disorder of energy utilization and storage, diagnosed by a co-occurrence of three out of five medical conditionsnamely abdominal obesity, elevated blood pressure (BP), elevated fasting plasma glucose, high serum triglycerides and low density cholesterol levels. Metabolic syndrome increases the risk of developing cardiovascular diseases particularly heart failure and diabetes. The principal symptom of metabolic syndrome is centralobesity (also known as visceral, male-pattern or apple-shaped adiposity), overweight with adipose tissue accumulation mainly around the waist and trunk.Other signs of metabolic syndrome include high BP, decreased fasting serum high density lipid (HDL) cholesterol, elevated fasting serum triglyceride level (VLDL triglyceride), impaired fasting glucose, insulin resistance, or pre-diabetes. Associated conditions includehyperuricemia, fatty liver (especially in concurrent obesity) progressing to non-alcoholic fatty liver disease (NAFLD),polycystic ovarian syndrome (PCOS, in women), erectile dysfunction (in men), and Acanthosisnigricans.[17]

## REVIEW OF LITERATURE

1. Pharmacognostical Studies on the Bark of Artocarpus hirsutus [4]
2. Pharmacognostical And Analytical Analysis Of Artocarpus Hirsutus.[5]
3. Themethanolic fruit extract of Artocarpus hirsutus was found to be effective in DPPHradical scavenging activity, hence having antioxidant activity.[6]
4. The ethanolic extracts of leaf, bark and wood of *A.hirsutus* showed strong anti-oxidant and tyrosinase inhibitory activityinvitro. [7]
5. The methanolic fruit extract ofArtocarpus hirsutus showed antimicrobial effect on bacterial strains viz., *Staphylococcus aureus*, *Bacillus subtillis,* and *Klebsiella pneumoniae.*[8]
6. Ethanolic extract isolated from both leaf and fruit of *Artocarpus hirsutus have* good active antifungal activity. It exhibited good inhibition activity against *A. tamarii, A. fumigates, A. flavus,* and *A. niger*.[9]
7. The antimicrobial efficacy of the aqueous extract of bark of Artocarpus hirsutus was proved against E.coli, Pseudomonas aeruginosaand Bacillus subtilis.[10]
8. The nanoparticles synthesized from boiled leaf extract of Artocarpus hirsutus by green route was found toxic against bacterial species revealed higher attributed activity against *Staphylococcus aureus andE.coli*.[11]
9. The ethanol extract of *Artocarpus hirsutus was* screened for its anti-inflammatory activity *in vivo,* it may be concluded that tender leaves of *Artocarpus hirsutus lam* possess significant anti-inflammatory activity[12]
10. The methanol extract of Artocarpus hirsutus exhibit significantinvivohepatoprotective activity and the histopathological studied proved the hepatic protection of extracts[13]

11. The ethyl acetate seed extract of *Artocarpus hirsutus* has shown that different doses of *Artocarpus hirsutus*exhibited a significant antihyperglycemic activity in diabetic animals[14]
12. The ethanolic extract of Artocarpus hirsutus leaves shows significant decrease inblood sugar levels and shows protective action on beta cells of the pancreas[15]
13. The aqueous extract of *Artocarpus hirsutus* fruits were evaluated for diuretic activity using modified Lipchitz method.[16]

**Main Objective**

To investigate the Phytochemical and Pharmacological Evaluation of seeds of *Artocarpus hirsutus* in the management of metabolic syndrome.

**Specific Objectives:**

- Pharmacognostical Evaluation
    - Histology of seeds of Artocarpus hirsutus.
- Phytochemical Evaluation
    - Preparation of nine extracts of Artocarpus hirsutus
    - To study the phytochemical composition of Artocarpus hirsutus
    - Seed extract by chemical tests, High-PerformanceThin Layer Chromatography (HPTLC) and Gas Chromatography(GS).
- Evaluation of Antioxidant activity and Detection of Phenolic compounds of Artocarpus hirsutus seed extracts.
- Pharmacological Evaluation
    - Evaluation of invivoanti-diabetic activity of Artocarpus hirsutus Seed extract in Streptozotocin- induced Wistar rats.
    - Evaluation of invivohypocholesterolemic potential of Artocarpus hirsutus seed extract in Wistar rats

## MATERIALS AND METHODS

### PLANT MATERIAL:

The seeds of Artocarpus hirsutus were collected and authenticated by Dr. UsmanArerath, young scientist(SERB-DST), Department of botany, MES KalladiCollege, Mannarkkad, Palakkad, kerala.

### EXTRACTION AND ISOLATION

The seeds of Artocarpus hirsutus were air dried and half of the seeds were roasted and the remaining seeds are non-roasted. Then both the roasted and non-roasted were powdered and later extracted with solvents like Hexane, toluene, Petroleum ether, Chloroform, Ethylacetate, Acetone, Ethanol, Methanol and Water.

### PHYTOCHEMICAL SCREENING

All the extracts were subjected to preliminary phytochemical qualitative and quantitative screening for the presence or absence of various primary and secondary metabolites such as test for alkaloids, glycosides, phenolic compounds and tannins, phytosterols, carbohydrates, saponnins and proteins.

### HPTLC FINGERPRINTING ANALYSIS

HPTLC fingerprinting studies were performed. Various concentrations of all extracts were prepared and used for HPTLC analysis. The test solution (2µg/ ml) were then loaded on pre-coated TLC plates (silicagel 60, $F_{254\ TLC}$ plates) with band length 6mm using a CAMAG LINOMAT 5 Automatic sample spotter.

Mobile phase Toluene: Ethyl acete:formic acid (5:3.5:0.5)

Detecting Agent: 2% FERRIC CHLORIDE SOLUTION IN ETHANOL (105°C for 5min)

## ANTI OXIDANT ACTIVITY

The anti oxidant activity of Artocarpus hirsutus seeds was determined by invitro method such as DPPH Free Radical Scavenging assay method. 0.1mM solution of 1, 1-diphenyl-2-picryl-hydrazyl (DPPH) in methanol was prepared and 1mL of this solution was added to 3 ml of the solution of all extracts in methanol at different concentration (50,100,200,400 & 800μg/mL).The mixtures were shaken vigorously and allowed to stand at room temperature for 30 minutes. Then the absorbance was measured at 517 nm using a UV-VIS spectrophotometer. Ascorbic acid (1-100 μg/ml) was used as the reference. Lower absorbance values of reaction mixture indicate higher free radical scavenging activity.The capability of scavenging the DPPH radical was calculated by using the following formula.

DPPH scavenging effect (% inhibition) = {(A0 –A1)/A0)*100}

## ANTI DIABETIC ACTIVITY

The objective of the study titled "Evaluation of Anti-diabetic activity of *Artocarpushirsutus*seed extract in Wistar rats" was to assess antidiabetic potential of *A. hirsutus* seed extract.

Male wistar Albino rats were utilized in this study. Animals were maintained under standard laboratory conditions (22 ± 3ºC room temperature and 50-60% humidity) with alternating light and dark cycles of 12 hrs. The rats were fed with pellet diet *ad libitium*and were acclimatized to laboratory conditions for 7 days prior to the experiment.

Induction of diabetes was done 24 rats using single intra-peritoneal injection of 30 mg/kg body wt. Streptozotocin (STZ) dissolved in freshly prepared citrate buffer (0.1 M, pH 4.5).Animals with fasting blood glucose over 200 mg/dL, three days after Streptozotocin administration were considered diabetic and they were divided into five groups of 6 rats each and received treatment.

Treatment related changes in body weights were recorded. Estimation of blood glucose levels was conducted on weekly basis. After completion of treatments, all

animals were fasted overnight and Oral Glucose Tolerance Test (OGTT) was conducted. Fasted rats were euthanizedon next day by overdose of Thiopental sodium injection (intra-peritoneal, i/p). Blood samples were collected immediately, by cardiac puncture and allowed to clot for 30 min at room temperature. Serum separated by centrifugation and used for hormonal and various biochemical estimations.The pancreas was collected and used for the histopathological analysis.

**ANTI-HYPERLIPIDEMIC ACTIVITY**

The objective of this study titled "Evaluation of Hypocholesterolemic potential of *Artocarpus hirsutus* seed extract in Wistar rats" was to assess potential of *A. hirsutus* seed extract to alleviate high fat diet induced hypercholesterolemia in laboratory rats. Male Wistar Albino rats were utilized in this study. Animals were maintained under standard laboratory conditions (22 ± 3ºC room temperature and 50-60% humidity) with alternating light and dark cycles of 12 hrs. The rats were fed with pellet diet *ad libitium,* acclimatized to laboratory conditions for 7 days prior to the experiment and were divided into five groups of 6 rats each and received treatment .

Hypercholesterolemia was induced in all animals, except normal control group, using High Fat Diet (HFD). Treatment related changes in body weights were recorded. After completion of treatments, all animals were fasted overnight. Fasted rats were euthanized on next day by overdose of Thiopental sodium injection (intraperitoneal, i/p). Blood samples were collected immediately by cardiac puncture and allowed to clot for 30 min at room temperature. Serum separated bycentrifugation and used for the estimation of biochemical parameters like lipid profile, AST, ALT and ALP. The liver was collected immediately followed by fixation in 10% (w/v) buffered formalin and used for histological studies.

## RESULTS AND DISCUSSION

### MACROSCOPIC STUDY

The seeds were pearl white , smooth and shining. It was elliptical in shape, 19mm long and 5mm thick. The hilum was prominent, circular at subterminal part of the seed. The raphae was dark brown and 4mm long. A thick seed encloses the entire cotyledons. The upper and dorsal surface was convex and concave respectively.

### MICROSCOPIC STUDY

TS passing through the centre of the seed was circular, shows thin layer of Arillus encircling the narrow brown colouredtestaand centrally located unequal sized horizontally placed cotyledond occupying the major area of the section.

The seed consists of a thick seed coat or testa, which measures 200µm in thickness. The testa uniformly thick all around the seed. The seed coat is differentiated into outer parenchymatous known as sarcotesta which includes polygonal thin walled parenchyma cells in the outer part. The cells become gradually polygonal thick walled cells towards interior. There are small prominent and well developed vascular strands located in thesarcotestaregion. The vascular strands include a few vertical rows of wide, angular and thickwalled xylem elements and thin layer of phloem elements.

### PHYTOCHEMICAL ANALYSIS

Artocarpus hirsutus plant is rich in major phytochemical compounds, especially rich in polyphenolic compounds. The qualitative phytochemical analysis of roasted and non roasted seed extract of Artocarpus hirsutus is presented in Table 1 and 2.

Qualitative analysis revealed the presence of phenolic compounds, Tannins, Phytosterols, Carbohydrates and Proteins. The findings and results of this study encourages for furthur potent activities.

## HPTLC PROFILE

HPTLC fingerprints were developed for all extracts in various solvent system with changing to verify the chemical constituents present.

HPTLC of seed extract was carried out and shows Rf value 0.47 and 0.45 of roasted and non-roasted ethanolic extract respectively compared with gallic acid as standard with Rf value 0.35.

## ANTIOXIDANT ACTIVITY- DPPH Scavenging Activity

Only non-roasted Ethanol, Water, and Methanol extract having high Antioxidant activity with 90.06%, 72.46% and 56.24% respectievely.

## ANTI DIABETIC ACTIVITY

### Body weight measurements

STZ-induced diabetic control rats showed significant reduction in body weight ($p < 0.05$)at 1st week itself after the STZ treatment compared to normal control rats, which remained at the lower side at 2, 3 and 4 weeks after the STZ treatment. At 4 weeks after the STZ treatment, average body weight of normal control and STZ (Group 2) rats were 295.83 ± 7.46 and 208.75 ± 27.57g, respectively ($p < 0.01$). On the other hand treatment with seed extracts of *Artocarpus hirsutus* in diabetic rats did not show any significant difference in body weight compared to normal control animals. At 4 weeks after the STZ treatment, average body weight of *A. hirsutus* seed extract(150mg/kg bwt.), *A.hirsutus*seed extract (300mg/kg bwt.) and glibenclamide (standard drug) groups were 266.25 ± 4.41, 252.50 ± 7.50, and 258.75 ± 15.05 g, respectively.

Diabetic rats showed a significant increase in the levels of blood glucose when comparedto normal rats. Oral administration of *A. hirsutus* seed extract, at 150mg/kg bwt. and 300mg/kgbwt., showed a significant reduction in the blood glucose level starting at the 21st day of treatment,compared to before treatment (day 1) as well as compared to the control values of diabetic rats in the corresponding days. This reduction, by *A. hirsutus*

seed extract, 150mg/kg bwt. and 300mg/kgbwt., was marked on the 28th day as reaching 51% and 36% reduction respectively, compared to day 1, and a 48.5% and 32% reduction respectively, compared to the control values of the diabetic group. Similarly,glibenclamide treatment of diabetic rats showed a significant reduction in blood glucose level on the 21st day of treatment, compared to before treatment and compared also to the control values of diabetic rats in the corresponding days. The glucose level was reduced by 52%compared to day 1 and 49% compared to control values of the diabetic group on the 28th day.

**Oral Glucose Tolerance Test (OGTT)**

Oral glucose tolerance test were performed to evaluate the anti-hyperglycemic effect of seed extracts of *A. hirsutus* on STZ-induced diabetic rats. The rats in the diabetic control group had a significant elevation in blood glucose level throughout the total measurement period (240 min)with respect to normal control; moreover, it did not come back to the initial value (0 min level) even at the end of the period tested. Area under curve (AUC) calculated from OGTT blood glucose concentration, which was also higher in STZ-induced diabetic control rats compared with normal rats ($p < 0.001$). On the other hand treatment of diabetic rats with glibenclamide or *A.hirsutus*seedextract induced a significant reduction in AUC relative to the diabetic control group. ($p<0.001$, glibenclamide and *A.hirsutus*seed extract (150mg/kg bwt., $p<0.01$, *A.hirsutus*seed extract(300mg/kg bwt.).

**Serum Biochemistry**

The STZ induced diabetic control group had significantly ($P<0.01$) higher serum glucose level compared to normal group. After four weeks of treatment, the diabetic rats that received *A.hirsutus*seed extract and glibenclamide had significantly reduced blood glucose concentrations compared with diabetic control group.

Diabetic rats showed a significant increase in the blood levels of TC, TG, and LDL. On the other hand, HDL was significantly reduced when compared to the values of normal control rats. Oral administration of glibenclamide significantly decreased the

blood levels of TC, TG and LDL.However,Glibenclamide did not significantly change the level of HDL, when compared to diabetic control rats. The treatment with *A.hirsutus*seed extract significantly decreased the levels of TC and LDL; however, there was no significant difference in the level of TG and HDL when compared to the values of the diabetic control rats.The concentration of serum biomarker enzymes, AST and ALT, was increased in diabetic rats when compared with normal control. Administration of *A.hirsutus*seed extract and glibenclamide reduced these levels compared to diabetic rats. Significant reduction was noted inserum protein levels of diabetic rats compared to normal control. However, treatment with *A.hirsutus*seed extract (150mg/kg bwt.) and glibenclamide (5mg/kg bwt.) effected significant elevation in total protein levels compared to diabetic control rats ($p<0.05$ and $p<0.001$respectively).

**Serum Insulin Assay**

The serum insulin level was significantly reduced in the diabetic group. Treatment of diabetic rats with *A.hirsutus*seed extract or glibenclamide for 4 weeks significantly increased the insulin level compared to diabetic control rats ($p<0.001$).

**Histopathological evaluation**

Histological examinations of the rat pancreas sections with (H & E) stain under lightmicroscope were conducted. In the pancreas of normal control rats, many round and elongated islets were evenly distributed throughout the cytoplasm, with their nucleus lightly stained than the surrounding acinar cells. In diabetic rats, the islets were damaged, shrunken in size and infiltration of lymphocytes was observed. In most of the rats treated with *A. hirsutus* seed extracts and standard Glibenclamide, islets were almost comparable to normal rats and there was not much shrinkage in size of the islet although slight damage was observed.

## ANTI-HYPERLIPIDEMIC ACTIVITY

### Body weight changes and liver weight measurements

HFD control rats showed marked increase in body weight during treatment period compared to normal control rats, but was not found to be statistically significant. At 4 weeks after treatment, average body weight of normal control and HFD (Group 2) rats were 295.83 ± 7.46 and 346.250 ± 17.002g, respectively. Similarly, treatment with seed extracts of *Artocarpus hirsutus* in HFD fed rats did not show any significant difference in body weight compared to normal control animals. At 4 weeks after the treatment, average body weight of *A. hirsutus* seed extract (150mg/kgbwt.), *A.hirsutus*seed extract (300mg/kg bwt.) and Atorvastatin (standard drug) groups were 300.625 ± 11.078, 304.375 ± 12.227, and 320.000 ± 17.440 g, respectively.

During 2nd week of treatment there was significant elevation in the body weight gainpercentage of HFD control rats (12.393%, $p<0.001$), *A. hirsutus* seed extract (low and high dose) treated rats (11.746% and 12.190% respectively, $p<0.001$) and Atorvastatin treated rats (10.648%,$p<0.001$), when compared to normal control rats (3.476%). However, during subsequent weeks there observed no significant difference in percent body weight gain among different treatment groups compared to normal and HFD control groups.

On sacrifice significant increase in liver weight was noted in HFD control rats (11.37 ±0.82, $p<0.001$) compared to normal rats (7.78 ± 0.142). However, treatment with *A.hirsutus*seedextract**,** at 300mg/kg bwt., effected significant reduction in rat liver weight (7.97 ± 0.338)compared to HFD control animals. *A. hirsutus* seed extract (150mg/kg bwt.) and Atorvastatin treated animals also showed marked decrease in absolute weight of liver and was comparable with that of normal control rats. Relative weight of liver was found to be elevated in HFD control rats (3.308 ± 0.207, $p<0.01$) compared to normal rats (2.62 ± 0.054). However, treatment with *A.hirsutus*seed extract (300mg/kg bwt.) resulted in statistically significant difference in relative liver weights of rats from HFD control animals.

### Serum lipid profile

In the present study, there was a significant elevation in the Total Cholesterol (TC),Triglyceride (TG) and Low Density Lipoprotein (LDL) levels in high fat diet inducedhypercholesterolemic (HFD control) rats (125.875 ± 2.481, 116.650 ± 11.919 and 53.395 ± 3.696 respectively) compared to normal diet fed rats (66.267 ± 3.914, 63.133 ± 6.588 and 1.523 ± 0.804 respectively). The treatment with *A.hirsutus*seed extract and atorvastatin significantly decreased the levels of TC, TG and LDL compared to HFD control rats; specifically treatment with *A.hirsutus*seed extract A (300mg/kg bwt.) resulted in significant reduction in TC and TG levels in high fat diet fed rats (47.550 ± 6.450 and 46.650 ± 3.750 respectively). However, there was no significant difference in the level of HDL among different groups when compared to the values of the normal control rats.

**Serum Liver function enzymes**

HFD control rats showed a significant increase in the serum biomarker enzymes, AST,ALT and ALP ($p<0.05$) when compared to the values of normal control rats. Oral administration of atorvastatin significantly decreased the serum levels of AST and ALT. Treatment with *A.hirsutus*seed extract A (300mg/kg bwt.) effected significant reduction in ALT levels when compared to HFD control rats. However, AST levels were not much reduced among *A.hirsutus*seed extract treated animals. Also there was no significant difference in the level of ALP among different groups when compared to the values of the HFD control group.

**Gross and Histopathological evaluation**

On gross examination, moderate fatty change was noted in the liver of HFD control rats. However, all normal control group rats and most of the treatment group animals showed almost normal appearance of liver. Histological examinations of the rat liver tissue sections with (H &E) stain under light microscope were conducted. Liver tissue of normal control rats, showed normal architecture with radiating appearance of hepatic chords. In HFD control rats, the normalstructure of liver was lost and most hepatocytes contained numerous fat vacuoles within cytoplasm(fatty infiltration). Central vein and portal triad were dilated; Sinusoidal spaces appear compressed. In most of the

rats treated with *A. hirsutus* seed extracts and standard Atorvasatatin, normal architecture of hepatic tissue was almost regained; there was marked reduction or almost absence of fat vacuoles within the hepatocytes in most of the treatment groups.

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